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September 16th 1999

Documents Management Branch (H.F.A. 305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville MD 20852
U.S.A.

Dear Sir/Madam

A. I refer to the statement (in CFR Part 101, Docket No.98P-0683) dated August 23, 1999 that "if the agency issues a proposed regulation on a health claim petition, the agency is to complete the rule-making within 540 days of the date the agency receives the petition ... therefore the F.D.A. finds that there is good cause under 21CFR 10.40(b)(2) to provide 30 days rather than 60 days for public comment on this proposal."

I wish to appeal the reduced petition time. The only reason given for the truncated petition time (from 60 days to 30 days) was that the document above was not filed earlier in a timely fashion. When the F.D.A. called for public submissions on the original proposal the "cut-off" date was (at the latest) the end of January. No new submissions or evidence after that date other than that of F.D.A. origin (or from published scientific documents accessed by the F.D.A.) was acceptable. I can find no good reason why the public's right to know of, and comment on, the revised proposals should be curtailed because of late filing by the F.D.A.: It is the F.D.A.'s responsibility to file in a timely fashion to enable U.S. citizens domiciled abroad, or interested overseas consumer representatives to have the time to have their say, otherwise citizens' or consumers' rights are diminished without due cause.

B. **THE** F.D.A. invites comments on specific technical points (1 through 4). I shall comment on (1) and (3) as follows:

(1) Comments were invited on:

> "Whether the proposed collection of information is necessary for the proper performance of F.D.A.'s functions, including whether the information will have practical utility; ..."

(a) The F.D.A. explains food bearing health claims must be authorised by the F.D.A. in response to a petition. They also advise that the process for petitioning the agency is described in Section 101.70(a), and information that the petition must include is described in Section 101.70(f). Please note the conditions required below (emphasis added):

> "A. Preliminary requirements. A complete explanation of how the substance conforms to the requirements of S.101.14(b) (21 CFR 101.14(b)). For petitions where the subject substance is a food ingredient or a component of a food ingredient, **the petitioner** should compile a comprehensive list of the specific ingredients that will be added to the food to

98P-0683

C145

supply the substance in the food bearing the health claim. For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of S.101.14(b)(3)(ii), e.g. that its use is generally recognised as safe (GRAS), listed as a food additive or authorised by a prior sanction issued by the agency, and what the basis if for the GRAS claim, the food additive status, or prior sanctioned status.

Substance means a specific food or component of food regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs or other similar nutritional substances. ...

The claim is limited to describing the value that ingestion (or reduced ingestion) of the substance, as part of a total dietary pattern, may have on a particular disease or health-related condition;

If the substance is to be consumed at other than decreased dietary levels:

(i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in S.170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and
(ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

(iii) *Validity requirement*. FDA will promulgate regulations authorising a health claim only when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognised scientific procedures and principles), that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.
Analytical data that show the amount of the substance that is present in representative foods that would be candidates to bear the claim should be obtained from representative samples, using methods from the Association of Official Analytical Chemists (ADAC), where available. If no ADAC method is available, the petitioner shall submit the assay method used and data establishing the validity of the method for assaying the substance in food. The validation data should include a statistical analysis of the analytical and product variability.

(b) Protein Technologies International Limited (P.T.I.) identified the substance as a specific component of specific foods as "isoflavone containing soy protein". They specifically excluded forms of soy protein which do not contain isoflavones. Scientific documents were presented in support of the proposition that "isoflavone containing soy protein" was implicated in lowering total serum cholesterol levels; that other forms of soy protein were not capable of doing so. For ease of review, I provide the following quotes (emphasis added):

(i) Cover letter of P.T.I. petition:

"Preliminary Requirements: Data establishing that isoflavone containing soy protein products such as isolated soy protein, soy protein concentrate and soy flour conform to the requirements of 21 C.F.R. 101.14(b) in that they are commonly consumed foods that are generally recognised as safe (GRAS) based on common use in food prior to 1958.

Summary of Scientific Data: Data establishing that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognised scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience that a relationship exists between the consumption of certain isoflavone containing soy protein products and a reduced risk of coronary heart disease."

(ii) Preliminary Requirements:

"The Substance of This Petition is Soy Protein with Naturally-Occurring Isoflavones.

The petitioner submits that the substance of this petition be defined specifically as:

Soy protein containing the sum total (in aglycone units) of all 12 isomers of naturally-occurring isoflavones in amounts of no less than 2 mg/g of soy protein.

The summary will also establish the basis for the threshold level of soy protein and the accompanying level of isoflavones required to achieve the biological effect of cholesterol-lowering that has been associated with a reduction in risk of coronary heart disease.

Soy protein with naturally-occurring isoflavones fully conforms to the definition of "substance" as described in 21 CFR 101.14(a)(2) which states that to be eligible for a health claim, the substance must be a food or a component of a food, and that, in accordance with 101.14(b)(3)(i), the substance must achieve its effect through its use as a food or component of food, e.g. through its nutritive value, which is retained at the levels consumed to justify the claim.

A number of other sources of soy protein commonly consumed in the diet may or may not contain sufficient amounts of naturally-occurring isoflavones to effectively lower blood cholesterol levels. These include the traditional fermented and nonfermented soy foods such as tofu, tempeh, and miso.

A variety of other food ingredients are also derived from soybeans. Some of these ingredients do not contain protein, others may contain protein, but without sufficient amounts of naturally-occurring isoflavones to have a cholesterol-lowering effect."

(iii) Scientific Summary:

"... only soy protein that has been processed in a manner in which isoflavones are retained will result in cholesterol-lowering.

Specificity of the Hypocholesterolemic Effect of Soy Protein with Naturally-Occurring Isoflavones.

To specify that soy protein containing naturally-occurring isoflavones is the substance identified in this health claim petition, evidence is provided to support the position that the cholesterol-lowering effect observed with ingestion of food sources of soy protein can be attributed to this substance and is independent of changes in other components within the diet when soy protein is consumed.

With the exception of isoflavones, there is no convincing experimental evidence to support lipid-lowering effects of any one of the others of these non-nutritive components.

Because of the large impact of processing, the amounts of isoflavones found in different food sources of soy protein is variable. Consequently, a minimum level of isoflavones needs to be consumed within the soy protein fraction in order to obtain the full benefit of ingestion of soy protein on blood lipids and lipoproteins.

The study also demonstrated that the lipid-lowering response observed with ingestion of ISP was significantly related in a dose-dependent manner to the amount of isoflavones found naturally within the sources of soy protein consumed ($p<0.05$).

In establishing an effective daily level of intake of soy protein, it is also necessary to specify a minimum effective level of naturally-occurring isoflavones that must also be present to achieve the full lipid-lowering benefit from ingestion of soy protein. The results of the recently completed does-response study in humans indicate that this level is between 38.9 and 61.8 mg total isoflavones/aglycone units (Crouse et al, in submission). Expressed on a per gram of protein basis, the effective amount of total aglycone isoflavones is between 1.55 and 2.47 mg. The linearity of the relationship

between soy isoflavones and the magnitude of the lipid response was also established in this study. Consequently, the effective daily level of intake of isoflavones in aglycone units can be calculated based on linearity to be approximately 2.0 mg/g of soy protein. At this level, 2.0 mg/g protein, a 3.2% decline in total cholesterol (95% CI = -0.8 to –5.6) and a 4.5% decline in LDL cholesterol (95% CI = -1.5 to –7.4) would be expected (Figures 1 and 2). For individuals with LDL-cholesterol concentrations >160mg/dL, 25g soy protein with 2.0mg total aglycone isoflavones/g protein could be expected to produce a 7.7% decline in total cholesterol (95% CI = -4.8 to –10.7) and a 9.5% decline in LDL-cholesterol.

Qualifying Amounts of Soy Protein to Permit Claim

It is proposed that the amount of soy protein required to qualify an individual food to bear the soy protein and heart disease health claim be established at 6.25g per reference amount customarily consumed (RACC). This proposed qualifying amount was derived by dividing the effective daily level of intake of 25g of soy protein by a factor of 4 to reflect the four eating occasions, three meals and a snack, defined as the typical dietary patter of most Americans.

At an intake of 6.25g of soy protein, a minimum of 12.5mg of total aglycone isoflavones should also be present per RACC. It must be emphasized that the qualifying amounts of isoflavones are based on levels present naturally within the soy protein fraction."

(c) The F.D.A., in evaluation of the health claims made by P.T.I. stated (Nov.1998) that the "FDA is not persuaded that the isoflavone component of soy protein is a relevant factor to the diet-disease relationship."

(d) Therefore, "the narrow issue of the method F.D.A. will use to verify that foods bearing the required amount of soy protein" is irrelevant to the petition of P.T.I. which emphasizes that the "substance" is "isoflavone containing soy protein" and that only the protein containing "qualifying amounts of isoflavones" will result in the beneficial effects claimed.

(e) The F.D.A. has a mandate to consider and evaluate only the claims made for the petitioned "substance". It does not have the mandate to consider or evaluate any other "substance". The F.D.A. has ruled that the "substance" identified as the isoflavone component of soy protein" is not a relevant factor. And yet this is the substance which is the basis of P.T.I.'s petition. The F.D.A. has therefore, in effect, dismissed P.T.I.'s petition. The F.D.A. has no mandate to substitute (under this regulation) a different substance (i.e. soy protein per se) and suggest that a health claim to be enforced by measurement of soy protein per se in foodstuffs could be relevant to the health claims proposed by P.T.I. as specific to just one component of some soy protein foods. Thus I submit that "the proposed collection of information" will have no practical utility in the enforcement of the petitioner's submission which was for "certain isoflavone containing soy protein". Furthermore, since

> "If the claim pertains to a substance not provided for in S101.9 or S101.36 FDA will propose amending that regulation to include declaration of the substance."

The F.D.A. could inappropriately and in absence of due process, potentially give legal approval to two additives (i.e. isoflavones and soy protein isolate) which currently, and for good cause, do not have G.R.A.S. status.

(3) Comments were invited on:

"ways to enhance the quality, utility, and clarity of the information to be collected."

The F.D.A. is required, by statute, to ensure that:

(i) "The summary shall concentrate on the findings of appropriate review articles, National Institutes of Health consensus development conferences, and other appropriate resources materials. Issues addressed in the summary shall include answers to such questions as:

1. Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?
2. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?
3. Are there certain populations that must receive special consideration?
4. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

In addition the summary of scientific data shall include a detailed analysis of the potential effect of the use of the proposed claim on food consumption, specifically any change due to significant alterations in eating habits and corresponding changes in nutrient intake resulting from such changes in food consumption. The latter item shall specifically address the effect on the intake of nutrients that have beneficial and negative consequences in the total diet.

(ii) That:

"no substance is present in an inappropriate level as determined in the specific provision authorising the claim."

(iii) That:

"All information concerning adverse consequences to any segment of the population (e.g. sensitivity to the substance)."

was presented by the petitioner and is evaluated by the F.D.A.

(iv) That:

"The claim is complete, truthful and not misleading."

My comments in respect of (3) therefore are:

(a) The F.D.A. has already found that:

"... the petitioner's conclusions regarding the significance of soy isoflavones with respect to the observed cholesterol-lowering effects of soy protein were not supported by the available studies."

Therefore the F.D.A. must determine the exact alternative "substance" before any collection of information will have utility. Only then will "truthful claims" be "made on foods" (136 Congressional record 11, 12953, Oct.26, 1990, Statement of Representative Waxman.

(b) "Section 403(r) of the act requires that food bearing a health claim authorised by regulation on a petition to the agency ..."

The F.D.A. is not authorised (by this Act) to regulate on anything other than the petition by the agency. That is, it cannot "substitute" a variation on the claim and make a proposed (or actual) ruling on this substituted purpose. Therefore the "clarity of the information must relate to the petition.

(c) The F.D.A. is required to ensure the claim is complete. A search of literature will indicate that P.T.I. did not accurately include summaries of adverse effects and so was incomplete, and was also misleading. The utility of the information arising from a diligent search of scientific literature should result therefore, in the F.D.A. returning the petition to P.T.I. and in denying approval. Any petition found to be "incomplete" should be returned to the petitioner (Sec.101.70) and should be denied.

(i) I include below, in part, a recent decision of the Broadcasting Standards Authority of New Zealand, which, having the force and authority of a court decision, will illustrate that the P.T.I. petition was in fact misleading, because of its omission of "significant disagreement among the experts".

IN THE MATTER of the Broadcasting Act 1989
AND
IN THE MATTER of a complaint by

R.F. JAMES
of Whangarei

Broadcaster
TELEVISION NEW ZEALAND LTD

DECISION

Turning to standard G6, the Authority notes TVNZ's claim that the item was essentially a cooking demonstration and that such a programme would not be expected to outline the health risks of ingredients being used. This may well be so. However, when making claims about health benefits of ingredients which are themselves a matter of controversy, then the Authority considers that the broadcast should at least acknowledge the existence of that controversy. In this instance, the cooking demonstration involved the use of soy, and the claimed benefits of the product were promoted extensively. Those claimed benefits are a matter of contention and there is controversy. The Authority concludes that this raises questions of a "controversial nature" to which standard G6 applies.

The Authority notes that no effort was made on the programme to point out that there is significant disagreement among the experts about the claimed health benefits of soy. As these criticisms were not raised or discussed, the Authority concludes that the programme lacked impartiality and balance, and that the standard was breached.

For the above reasons, the Authority upholds the complaint that a segment on *Good Morning* on 3 May 1999, broadcast by Television New Zealand Ltd, breached standards G1 and G6 of the Television Code of Broadcasting Practice.

(ii) I also refer the F.D.A. evaluators to Figure 1, p.279 "Meta-analysis of the Effects of Soy Protein on Serum Lipids." Anderson et al, New England Journal Medicine, August 3, 1996. The net change for individuals in serum LCL cholesterol (from 31 trials) indicates that for some individuals, especially those subjects with initial normal levels, soy protein ingestion increased LDL levels. The complete study as published was provided by P.T.I. as a part of their submission.

Yours sincerely

Valerie James.

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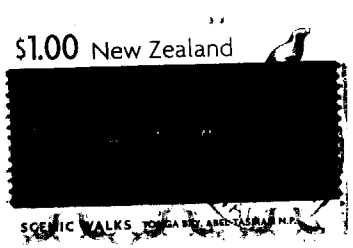

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